1: Dig Dis Sci. 1999 Mar;44(3):643-8. 

# Characterization of two novel proabsorptive peptide YY analogs, BIM-43073D and BIM-43004C.

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Effective clinical therapy to augment intestinal absorption of water and electrolytes does not exist; the gut hormone, peptide YY (PYY), is a potent proabsorptive agent in animal models. The purpose of our study was to evaluate the effects of two novel PYY analogs, BIM-43073D and BIM-43004C, on intestinal absorption. Dogs with ileal Thiry-Vella fistulae (TVF) were treated with either PYY, BIM-43073D, or BIM-43004C. Administratio of BIM-43073D significantly increased water and sodium absorption over baseline and maintained this level of increased absorption for a longer duration than an equimolar dose of PYY. Administration of BIM-43004C significantly increased sodium and water absorption over baseline at a level equal to that of PYY. The novel PYY analogs, BIM-43073D and BIM-43004C, are effective proabsorptive agents with BIM-43073D producing more sustained effects than PYY. These compounds may be clinically useful in the treatment of gut malabsorption in conditions such as cholera, Crohn's disease, and the short-bowel syndrome.

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Exhibit 3

1: J Med Chem. 2000 Sep 7;43(18):3420-7. Related Articles, Link

ACS PUBLICATIONS

# Structure-activity studies including a Psi(CH(2)-NH) scan of peptide YY (PYY) active site, PYY(22-36), for interaction with rat intestinal PYY receptors: development of analogues with potent in vivo activity in the intestine.

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Peptide YY (PYY) is a gut hormone that inhibits secretion and promotes absorption and growth in the intestinal epithelium. We have performed structure-activity studies with the active site, N-alpha-Ac-PYY(22-36)-NH (2), for interaction with intestinal PYY receptors. Investigation of aromatic substitutions at position 27 resulted in analogues that exhibited potent in vitr antisecretory potencies with N-alpha-Ac-[Trp(27)]PYY(22-36)-NH(2) exhibiting even greater potency than intact PYY. In vivo studies in dogs revealed that this analogue also promoted intestinal absorption of water and electrolytes during continuous intravenous and intraluminal infusion. Investigations carried out to identify features that would enhance stability revealed that incorporation of Trp(30) increased affinity for PYY receptors. A "CH(2)-NH" scan revealed that incorporation of reduced bonds at position 28-29 or 35-36 imparted greater receptor affinity. In general, disubstituted analogues designed based on the results of single substitutions exhibited goo receptor affinity with N-alpha-Ac-[Trp(27),CH(2)-NH(35-36)]PYY(22-36)-NH(2) having the greatest affinity (IC(50) = 0.28 nM). Conservative multipl substitutions with Nle-->Leu and Nva-->Val also imparted good affinity. An analogue designed to encompass most of the favored substitutions, N-alpha-Ac-[Nle(24,28),Trp(30),Nva(31), CH(2)-NH(35-36)]PYY(22-36)-NH(2), exhibited a proabsorptive effect in dogs comparable to, but longer lasting than, that of intact hormone. Selected analogues also exhibited good antisecretory potencies in rats with N-alpha-Ac-[Trp(30)]PYY(22-36)-NH(2) being even more potent than PYY. However, the potencies did not correlate well with the PYY receptor affinity or the proabsorptive potencies in dogs.

Exhibit 4

These differences could be due to species effects and/or the involvement of multiple receptors and neuronal elements in controlling the in vivo activity o PYY compounds. PYY(22-36) analogues exhibited good affinity for neurona Y2 receptors but poor affinity for Y1 receptors. Also, crucial analogues in this series hardly bound to Y4 and Y5 receptors. In summary, we have developed PYY(22-36) analogues which, via interacting with intestinal PYY receptors, promoted potent and long-lasting proabsorptive and antisecretory effects in in vivo models. These compounds or analogues based on them may have useful clinical application in treating malabsorptive disorders observed under a variety of conditions.

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